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Hypothesis review: The direct interaction of food nanoparticles with the lymphatic system

Wei Lu [a], Jingke Guo [b], Jianwu Zhou [b], Lijing Ke [b], Shutao Liu [a], Guanzhen Gao [a], Huiqin Wang [a], Wei Ding [a], Pingfan Rao [a,b,*]

[a] *Institute of Biotechnology Fuzhou University, Fuzhou 350002, China*

[b] *CAS.SIBS-Zhejiang Gongshang University Joint Center for Food & Nutrition Research, Hangzhou 310035, China*

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Abstract

Besides digestion and assimilation, there are other modes of direct interaction between food and human body. As it is known, the mucosal layer of the digestive tract interfaces with food after the digestion process. It has been demonstrated to uptake the micro- and nanoparticles via mucosa-associated lymphatic tissues (MALT). On the other hand, food is a typical polydisperse system and contains micro- and nanoparticles with different sizes and properties. Accordingly, it is hypothesized that food nanoparticles can directly interact with MALT and more specifically with the support of the preliminary experimental data from our research, that antioxidant nanoparticles can interact with the lymphatic vessels. This kind of interaction would be of great physiological importance. The confirmation of the hypothesis will establish a significant and novel approach to understand food system and provide answers to currently incomprehensible phenomena such as the biological functions of phytochemicals with low bioavailability.

Keywords: Food nanoparticles; Uptake; Intestinal mucosa; Lymphatic

1. Relationship between food and human body

There are many approaches to understand the relationship between food and human body. As elucidated by nutrition science, food is indispensable to life because of its role as the source of nutrients which are essential to support life and sustain growth. It is also a very important mean to maintain health and wellness, which has been scientifically demonstrated by ever increasing evidence in recent years. What is known more as common sense than scientific knowledge is that food is an important provider of sensory pleasure for human beings [1,2].

When food is considered as either the nutrient provider or a health keeper, it is known to be firstly physically, chemically, and biochemically broken down into the constituents and then be assimilated in the form of molecules which are subsequently circulated to organs, tissues and cells all over the body. One interaction mode of food with the body, already deeply studied, is degradation of intact food to polymers and molecules to interact with cells [3]. There is also a mode of direct interaction of food with the body without passing through the circulation system. It is mostly investigated as the sensory aspect of food. Free molecules can directly interact with cells to generate sensations, such as volatile molecules interact with cells of the olfactory organ resulting in sensory odors [4], and capsaicin binds to the heat-activated calcium channel protein on the heat sensing neuron to generate heat [5]. Otherwise, processing of food in the mouth contributes significantly to the sensory perception, which is one of the very few cases studied so far of non-molecular direct interaction of food with the body [6].

2. Interaction of food with human body via digestive tract mucosa

Referring to the interaction of food with human body, the digestive tract and the skin – the two major interfaces of human

* Corresponding author at: CAS.SIBS-Zhejiang Gongshang University Joint Center for Food & Nutrition Research, 149 Jiao Gong Road, Hangzhou 310035, China. Tel.: +86 139 60908904; fax: +86 571 88071204.

E-mail address: Pingfan.Rao@gmail.com (P. Rao).

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body interacting with external substances are discussed. The digestive tract and the skin are significantly different in their functions and structures due to the fundamental difference of the substances they are interfaced with. The former is a barrier and insulation, and functions as the first line of defense against the external harmful factors [7]. Whereas the latter is covered with a thin layer of permeable mucus rather than the tough and waterproof stratum corneum [8], the uppermost layer of the skin. Different from the substances the skin may be exposed to, those passing through the digestive tract can be anything but harmful. Different structures are ingeniously devised for different modes of interface with external substances. Apparently, the mucosal layer of the digestive tract functions not as insulation but facilitation of the interaction between food and the body in both digestion and assimilation course. The process is that food is firstly masticated and broken down in the mouth and then goes through various proteolysis in the stomach and further digestion and principle absorption in the intestine. Considering the interactive nature of mucosal layer and complex components of food before and after digesting process, there may be some other direct non-molecular interactions besides the known processes, which require further investigations.

Digestion imparts constant changes in the digestive tract thus mucosal layers in different sections of the tract are highly specialized, in order to carry out different interactions with ever changing food materials. A histological feature characterized by the mucosa layer from mouth to colon is the heavily populated with lymphoid cells and densely aligned lymphatic vessels. Mucosa-associated lymphoid tissues (MALT) are scattered along the wet mucosal linings throughout the digestive tract. Those surfaces constitute the most extensive immune barrier against pathogens [9]. Meanwhile, they are also the very venue for the direct interaction between the body and the external substances. This type of direct interaction will lead to the uptake of certain external substances, i.e. lipids, which are absorbed by human body through lymphatic system located in the intestinal tract.

3. Uptake of nanoparticles by digestive tract

Besides low molecular weight compounds, natural or synthetic micro- and nanoparticles can also be uptaken through the mucosa of the digestive tract. They can pass through the epithelial layer of digestive tract and passage into lymphatic vessels and lymph nodes and then deliver to various locations of the body. The earliest evidence of nanoparticle uptake was obtained from the observation that raw starch fed to rats was absorbed across the gut mucosa [10]. As a matter of fact, particles with different sizes ranged from nanometers to micrometers, natural or synthetic, metallic or organic, have been found to be uptaken across the mucosal layer of the digestive tract into the lymphatic system or blood [11]. Particles are transported across the epithelial mucus via one of the three possible routes identified, including paracellular penetration, endocytosis and uptake via mucosa-associated lymphoid tissues (MALT) depending on different sizes [12,13], surface charges [14], hydrophobicity level [15,16] and other factors [17]. The process is not only considered as a regular process [18,19], but also a promising novel approach to efficiently facilitate drug and vaccine delivery [20,21]. However, at present little is comprehensively understood about that the biological impact micro- and nanoparticles can generate when they are transported across the mucosal epithelia into the lymphatic system or further to visceral organs and tissues of the body.

4. Food nanoparticles

If food system contained micro- or nanoparticles with certain sizes and characteristics, which can be uptaken via lymphatic tissues of the digestive tract mucosa, they may possibly be uptaken in the same way. Hardly any substances can be better candidates than food as versatile micro-and nanoparticle providers for mucosal uptake. Food raw materials contain diverse compositions from free molecules to insoluble polymers, heat sensitive to insensitive proteins and hydrophilic to hydrophobic chemicals. They not only construct functional animal or plant bodies but also form the polydisperse system of food including solution, colloid, emulsion, foam, gel, etc. [22]. Processing such as heating, mechanical treatment and fermentation of food materials can accelerate chemical and physiochemical interactions between various compositions, resulting in even more diverse dispersions [23]. As a course of diminution, physical process, such as mixing with saliva or mastication of food, can possibly bring about more changes in dispersions besides biochemical process, i.e. enzymatic degradation. Therefore, the prominently diverse dispersions in raw materials together with further in vivo processing can possibly render food system containing micro-and nanoparticles of diverse properties. These micro- and nanoparticles are completely eligible to react with versatile mucosa linings of digestive tract.

The in vitro processing of food materials is different from the in vivo processing mentioned above and is also a course of food nanoparticles production. An insight into how processing generates food nanostructures has been gained from our recent work on soup [24]. Technically speaking, soups are products of boiling water and an extract of food materials, either animal or plant origin. It is found that only a certain substances actually migrate from the solid phase into the aqueous phase upon boiling water extraction. Besides water-soluble small molecules, lipid proteins in animal food materials and glycated protein in herbs resulted from Maillard reaction are found to migrate into soup, both of which can assemble into nanoparticles, respectively. Preliminary results indicate that those nanoparticles play a key role in maintaining biological activities of corresponding soups which are known as folk remedies [25]. Among all types of nanoparticles in a food system, only those which are physically and chemically stable can be expected to carry out meaningful reactions. Furthermore, nanoparticles obtained under harsh conditions, i.e. boiling water extraction, show outstanding physiochemical stable features and are likely to interact with mucosa layers, resulting in possibly reproducible impacts and endowing the food system with unique characteristics.

In a word, nothing is interfacing with the mucosal linings of digestive tract more than food, which is proved to be a typical polydisperse system, containing micro- and nanoparticles. The uptake of these nanoparticles undoubtedly predominate all the mucosal nanoparticles uptake events. However, hardly any mucosal uptake of food nanoparticles has been seriously investigated. The lipid absorption process in the intestine has been preliminarily proved in previous work [26]. It is considered as a typical process of food microparticles uptake into lymphatic system, but the mechanism behind has not been fully understood. If natural or synthetic polymers can all find their pathways into the lymphoid system, there is no reason for the mucosal layers not to become the venue to start the interaction of food nanoparticles and the lymphatic system. What has been learnt from the research on microparticle–mucosa interaction using defined model systems can be similarly applied to food-derived nanoparticles.

5. The hypothesis: direct interaction of food nanoparticles with MALT

The uptake of micro-and nanoparticles via route of MALT is a well established "regular process". On the other hand, food is a typical polydisperse system and abundantly contains nanoparticles with different sizes and characteristics. Thus, it is logical to hypothesize that food nanoparticles can directly interact with the MALT of digestive tract, leading to uptake of these nanoparticles. They are consequently delivered to various locations of the body and generate potential biological significances.

Among all the possibilities, the uptake of antioxidant micro- and nanoparticles into lymphatic vessels may be of the greatest biological importance. When the superoxide production exceeds the intracellular or extracellular antioxidant capacity due to oxidative stress, the excessive superoxide in the interstitial fluid can be removed by the lymphatic system as to collect and transport tissue fluids from the intercellular spaces back to the blood [27]. It is the lymphatic capillaries, but not the blood capillaries that receive the excessive superoxide from the interstitial fluid, due to the open end of the lymph vessel and the higher osmotic pressure in capillary [28]. The lymphatic system may thus function as a channeling or drainage of the interstitial superoxide and consequently be in need of antioxidants to secure its immune function. The mucosal uptake of antioxidant nanoparticles which exist in most herbal extracts will act as a direct external antioxidant role to the lymphatic system under oxidative stress. Although, the mechanism of how antioxidant nanoparticles directly mitigate the stressed status of the lymphatic system is unknown, it is reasonable to expect some significant effects on the immunity after the uptake of antioxidant nanoparticles into the lymphatic system via the mucosa.

Unconventional evidence on the direct interaction of antioxidant nanoparticles with lymphatic tissues has been obtained from our work on an herbal drink (data unpublished). The effect of ingesting the herbal drink on lymphatic tissues was monitored by determining voltage changes between the acupoints of Shaohai (HT3) and Shenmen (HT7) belonging to the heart meridian line. Ten minutes after the herbal drink was ingested, the voltage between Shaohai (HT3) and Shenmen (HT7) started to decrease while it remained unchanged in the group of the herbal drink

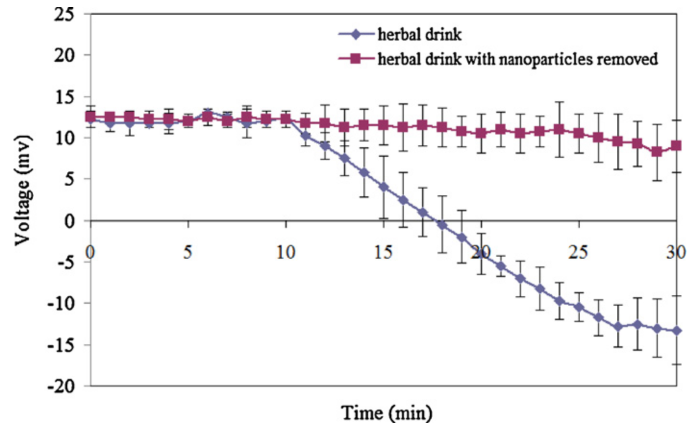

Fig. 1. The time course of voltage between Shaohai (HT3) and Shenmen (HT7) after ingestion of herbal drink. *Subjects: 16 healthy young adults were randomly divided into two groups (herbal drink and herbal drink with nanoparticles removed) and each of them ingested the herbal drink with or without nanoparticles. Ingestion volume: 660 ml (two cans). Measurement: body surface potential between acupoints of Shaohai (HT3) and Shenmen (HT7) after ingestion. Instrument for body surface potential determination: voltage meter of model USB-6281 (National Instruments, USA) and disposable ECG electrodes (Ag/AgCl). The final result is shown in this figure.

with nanoparticles removed (Fig. 1). In our previous work [29], acupuncture meridians were revealed as the superoxide channel where superoxide traveled through in the form of electrons driven by the voltage differences. The changes of voltage differences between two acupoints along a specific meridian line can reflect the amount change of the superoxide discharged from the visceral organ that the meridian is connected to. Therefore, it suggests that nanoparticles in the herbal drink can change the superoxide level of the cells and lead to voltage changes between related acupoints. Moreover, all of the experimental subjects ingested the herbal drink behaved more peaceful and relaxed, which is in coincidence with the traditional function of the drink as Chinese herbal tea. Although many questions remain unknown in the results, what is inspiring is that the importance of particles is confirmed that the interaction is not a conventional assimilation process which requires much longer time, and the interaction did influence the superoxide channels and cause remarkable serum biomarkers level changes [30].

6. Prospect

It is apparent that the elucidation and establishment of the direct interaction of food nanoparticles with the lymphatic is a formidable undertaking. It requires concerted multidisciplinary approaches of biochemistry, immunology, physiology, histology, food science, colloid science, nanotechnology, etc. The efforts, however, will be worthwhile. Long existing puzzles will be solved, such as why most phytochemicals can take effects with little or no bioavailability [24]. A new supermolecular approach will be established to understand food health function, which is a model closer to the real food complex system than the single compound approach currently employed.

What is most inspiring is that if the mechanism of food unique function to influence health is elucidated, it will uncover the myth of the traditional accumulated history of our people about food and health. Food will become not only a probe to understand life, but also the potential medicine for health.

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